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Meeting report

Erratum to 'The management of chronic hepatitis B in the immunocompromised patient: Recommendations from a single topic meeting' [J. Clin. Virol. 41 (4) 2008 243–254]

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Abstract

Patients with chronic hepatitis B virus (HBV) infection have a substantial risk of reactivation and jaundice following the use of immunosuppressant therapy. A single topic conference was convened to discuss the management of HBV patients undergoing chemotherapy for haematological malignancy, liver and renal transplantation and with HIV co-infection. In advance of the meeting a draft guideline was prepared and circulated to a participating expert panel. Presentations and consensus views were obtained on the day of conference to allow pragmatic algorithms to be established on each of these topics.

Use of lamivudine prophylaxis for HBV patients undergoing chemotherapy and renal transplantation is strongly supported with good evidence. Patients with HBV cirrhosis who are candidates for transplantation should be started on nucleos(t)ide therapy prior to surgery and, in addition, hepatitis B immune globulin given from the time of transplantation onward. Co-infection with HBV and HIV offers unique challenges. If the patient is a candidate for highly active retroviral therapy then dual nucleos(t)ide analogues which are also active against HBV must be used to prevent immune reconstitution hepatitis. In all these conditions, awareness of possible HBV resistance to therapy must be kept in mind and HBV DNA levels monitored.

Keywords: Hepatitis B; Immunocompromised host; HIV; Kidney transplantation; Liver transplantation; Chemotherapy

1. Introduction

The management of chronic hepatitis B virus (HBV) infection in immunocompromised patients presents challenges above and beyond those routinely encountered in this already complex disease. With this in mind a single topic conference was convened jointly, in May 2007 by the Scottish Viral Hepatitis Group and the Scottish Diagnostic Virology Group to discuss the management of hepatitis B in the specific contexts of chemotherapy for haematological malignancy, liver and renal transplantation and HIV co-infection.

2. Methods and aims

The aim of the meeting was to generate pragmatic guidelines combining best available evidence and expert opinion. In advance of the meeting a discussion document containing draft guidelines was prepared and circulated to a participating expert panel. On the day of the meeting presentations

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were given on each of the topics followed by a panel discussion with questions from the floor. The discussions were transcribed and used to prepare the following guidelines which are presented in Figs. 1–4, and discussed here in turn.

2.1. Management of hepatitis B infection in patients undergoing chemotherapy for haematological malignancy (Fig. 1)

2.1.1. Background

Chemotherapy induced reactivation of hepatitis B is a well-recognised phenomenon first described over 30 years ago (Galbraith et al., 1975). It is thought that chemotherapy-induced immunosuppression allows a rapid increase in viral replication (Mindikoglu et al., 2006). Between cycles, or after cessation of chemotherapy, reconstitution of the immune system takes place. During this period a T cell-mediated immune response may occur against the increased number of infected hepatocytes with a clinical picture ranging from elevation of ALT, through jaundice, fulminant liver failure and death (Lok et al., 1991).

Whilst no uniform definition of reactivation exists one that is commonly used is the presence of hepatitis (as suggested by an ALT > 3ULN) in combination with either a 10-fold rise in HBV DNA viral load or an absolute value greater than 20,000 IU/ml. The risk of reactivation for HBsAg-positive patients undergoing chemotherapy for haematological malignancy is between 33% and 67% (Lok et al., 1991; Nakamura et al., 1996; Markovic et al., 1999; Yeo et al., 2005), with regimes containing high dose steroid or rituximab independently increasing risk (Cheng, 1996; Takai et al., 2005; Hui et al., 2006). Patient factors conferring increased risk include high serum HBV DNA pre-chemotherapy (Lau et al., 2002; Yeo et al., 2004), male sex and high levels of ALT.

Reactivation mortality rates have been reported variously as between 5% and 37% (Lok et al., 1991; Nakamura et al., 1996; Markovic et al., 1999), with more patients developing jaundice. The latter causes significant morbidity and may necessitate interruption of chemotherapy potentially leading to a poorer treatment outcome.

Although less common, reactivation may occur in patients who are HBsAg negative but positive for other markers of prior exposure to the virus, including anti-HBc or anti-HBs alone or in combination (Lok et al., 1991; Law et al., 2005; Hui et al., 2006). Although the reactivation rate is lower amongst this group, in the region of 5%, reactivation carries a significant risk of mortality and morbidity (Hui et al., 2006). In areas of low HBV endemicity up to 20% of patients with markers of prior exposure to HBV will have anti-HBc in isolation, which may represent acute infection, occult infection, resolved distant infection or a false positive result (Grob et al., 2000). Those with occult HBV infection, defined as HBsAg negative with low-level detectable HBV DNA, appear to have the greatest risk (Hui et al., 2006).

2.1.2. Screening of patients undergoing chemotherapy

Given the high rate of reactivation and subsequent morbidity/mortality amongst patients with chronic hepatitis B undergoing chemotherapy it is recommended that all patients undergoing chemotherapy for haematological malignancies have their HBV status assessed by testing for serum HBsAg and anti-HBc. The rate of HBV infection may be higher amongst patients with haematological malignancy than in the background population (Pioltelli et al., 2000; Kim et al., 2002; Talamini et al., 2004; Marcucci et al., 2006) and screening is cheap and widely available.

2.1.3. Evaluation of HBsAg-positive patients

HBsAg-positive patients should have their serum HBV DNA levels checked. Those patients with HBV DNA levels >2000 IU/ml should be evaluated further with regards to serum ALT, e-antigen status, liver biopsy or non-invasive markers of fibrosis (Myers et al., 2003), and considered as potential candidates for treatment rather than prophylaxis. These patients are at highest risk of reactivation on withdrawal of prophylaxis (Lau et al., 2002; Yeo et al., 2004) and indefinite therapy may be required.

2.1.4. Prevention of reactivation

Prophylaxis strategies against hepatitis B reactivation have concentrated on the nucleoside analogue lamivudine, with less published data concerning newer nucleos(t)ide analogues. Interferon-α is unlikely to be tolerated in patients undergoing chemotherapy due to its side effect profile.

Good evidence exists that pre-emptive (started before chemotherapy introduced) lamivudine prophylaxis prevents reactivation of hepatitis B in HBsAg-positive patients undergoing chemotherapy, with a systematic review identifying a reduction in reactivation rates of between four and sevenfold (Kohrt et al., 2006). The same analyses found excellent tolerability and safety of lamivudine in patients undergoing chemotherapy, with no significant adverse drug effects.

The available data suggests prophylaxis is superior to delaying treatment until serological evidence of reactivation is detected (Lau et al., 2003) and it is therefore recommend that all HBsAg-positive patients undergoing chemotherapy receive nucleoside analogue prophylaxis. Whilst lamivudine has the largest body of evidence in the setting, newer analogues such as adefovir and entecavir are likely to be equally effective. Given the improved resistance profile of such drugs, it is likely that as experience with such drugs grows, they will succeed lamivudine as first line prophylactic therapy in this setting.

2.1.5. HBsAg-negative patients with markers of HBV infection

As HBsAg-negative patients are at lower risk of reactivation different strategies have been advocated to avoid the need for universal prophylaxis. The most promising of these

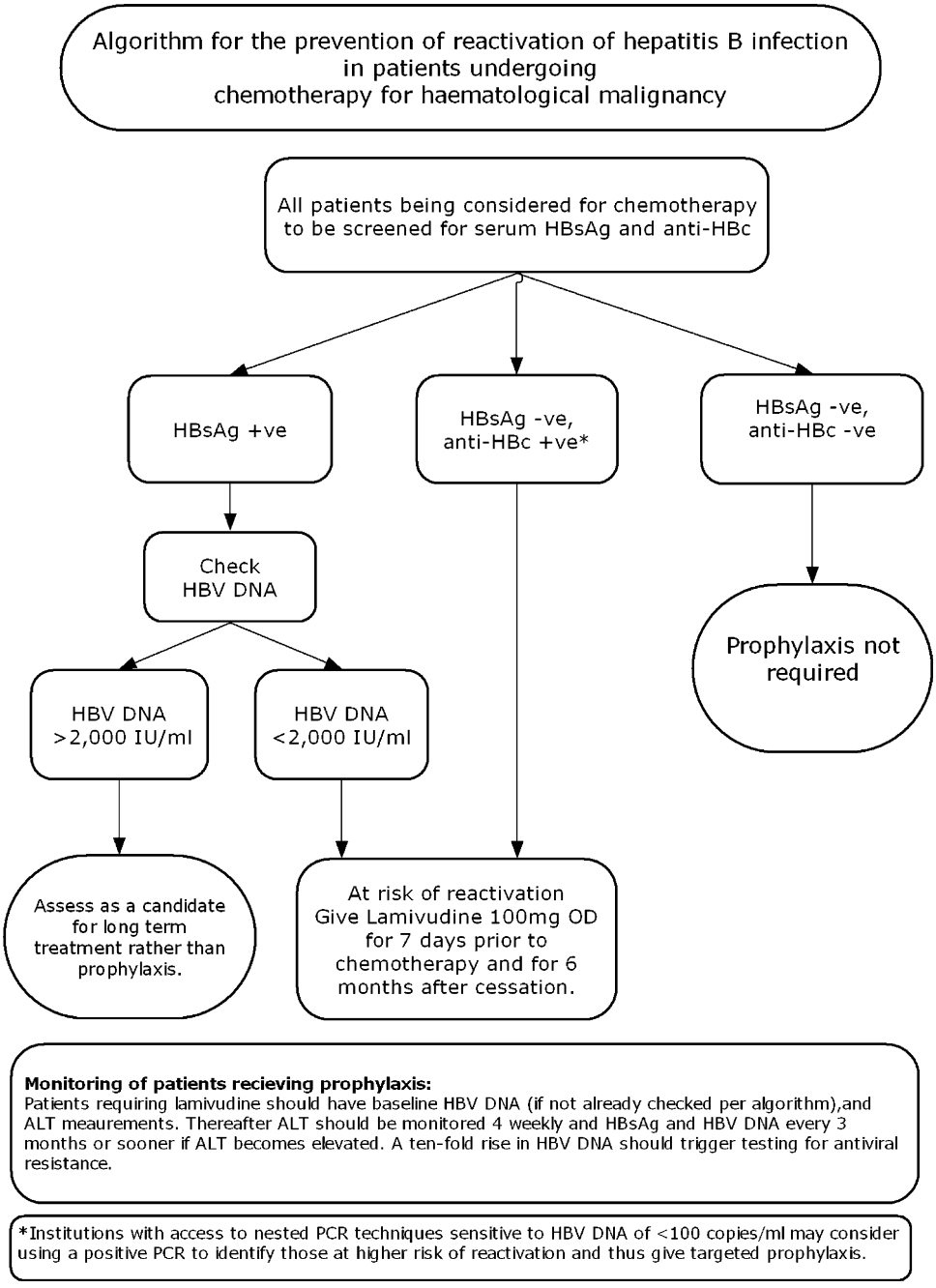

Fig. 1. Algorithm for the prevention of reactivation of hepatitis B infection in patients undergoing chemotherapy for haematological malignancy.

is the use of sensitive HBV DNA assays to identify those with isolated anti-HBc that have occult infection. Unfortunately at risk patients will often have DNA levels of less than 100 copies/ml, and in some cases DNA will only be detectable by nested PCR techniques (Hui et al., 2006). As the assays required for such a strategy are largely unavailable in routine practice it was not felt that such an approach could be routinely recommended. In future this may become the preferred option, and institutions with current access to adequately sensitive assays may wish to pursue such a strategy.

A strategy of fortnightly HBV DNA estimations and instigation of prophylaxis only in the event of a 100-fold rise in DNA (Hui et al., 2006) could not be recommended due to several issues. These include unproven cost effectiveness, difficulties ensuring adequate supervision of patients outwith a clinical trial setting, and a lack of a prospective trial to establish that such an approach is effective both in preventing adverse outcome and reducing the number of patients requiring prophylaxis.

Other recommendations have included vaccination of isolated anti-HBc-positive patients with a single dose of HBV

vaccine to induce anti-HBs, and to exclude those patients with an antibody response from prophylaxis (Lalazar et al., 2007). It is known that, at least in HBV naïve patients, vaccine is less effective in those with haematological malignancy (Weitberg et al., 1985; Goyal et al., 1998) and in the absence of a prospective trial of such an approach it is unclear how many patients would avoid prophylaxis. Given this, together with evidence that anti-HBs is not uniformly protective of reactivation (Hui et al., 2006) it was not felt that such an approach could be recommended.

Given the excellent safety profile of lamivudine in the context of chemotherapy it is felt that any risks of unnecessary treatment are outweighed by the benefits of ensuring all at risk patients are treated. Equally it is important that any guideline does not introduce undue delay or confusion into a situations were timely treatment is of the essence. It was therefore agreed that nucleoside analogue prophylaxis be given to all HBsAg-negative patients who are anti-HBc-positive, although in time wider availability of more sensitive assays may more readily identify those truly at risk.

2.1.6. Duration of prophylaxis

Prophylaxis is recommended to start 7 days prior to commencing chemotherapy and to continue for 6 months after cessation of chemotherapy, although both figures are arbitrary and further work is required on the optimal duration of treatment. Patients should have their ALT monitored every 4 weeks during prophylaxis, with HBsAg and HBV DNA testing every 3 months or if serum ALT is elevated. As in other settings a greater than 10-fold rise in HBV DNA above the nadir should trigger testing for resistance to lamivudine or other prescribed nucleos(t)ide. Due to a risk of recurrence after withdrawal of prophylaxis, monitoring should continue for 1 year after cessation of therapy.

2.1.7. Non-haematological malignancy and patients with chronic inflammatory conditions

Although published experience is more limited, HBV reactivation is recognised amongst patients undergoing chemotherapy for non-haematological malignancy. Yeo et al. (2004) reported reactivation rates varying between 6.9% for gastrointestinal cancers and 41% for breast carcinoma. The authors reported an increased risk amongst patients receiving anthracyclines and steroids (both commonly used in the treatment of haematological malignancies), suggesting that the degree of immunosuppression induced may be more important than the underlying malignancy. Therefore, decisions regarding prophylaxis for solid organ tumours should be individualised, based on the proposed chemotherapy regimen.

Amongst patients receiving immunosuppression for chronic inflammatory conditions, such as rheumatoid arthritis and inflammatory bowel disease, reports of reactivation of hepatitis B are increasingly recognised. Agents implicated include both traditional treatments such as methotrexate and corticosteroids, and the newer anti-TNFα biological agents (Esteve et al., 2004; Calabrese et al., 2006). These case reports include several deaths resulting from hepatic failure, and whilst the absolute risk remains unclear, nucleos(t)ide analogue prophylaxis should be considered in HBsAg-positive patients commencing such therapy, with close monitoring of any patients not receiving prophylaxis.

2.2. Hepatitis B and liver transplantation (Fig. 2)

2.2.1. Background

Prior to the introduction of hepatitis B immunoglobulin (HBIg) liver transplantation (LT) in patients with hepatitis B was associated with a high rate of graft re-infection, which in the context of immunosuppression led to rapidly progressive liver disease (Todo et al., 1991; Samuel et al., 1993). Mortality in the pre-HBIg era was high with a 5-year survival rate of between 40% and 60% (Todo et al., 1991; Samuel et al., 1993). With the introduction of HBIg monotherapy and subsequently combination therapy with HBIg and lamivudine, graft re-infection rates were dramatically reduced and outcomes for HBV infected patients began to match or even exceed other transplant indications (Kim et al., 2004).

2.2.2. Management of HBV cirrhosis prior to transplantation

Patients with HBV DNA titres in excess of 2000 IU/ml are at increased risk of disease progression (Iloeje et al., 2006) and hepatocellular carcinoma (HCC) (Chen et al., 2006). Likewise suppression of viral replication may lead to an improvement in liver function and survival and in some cases obviate the need for transplantation (Perrillo et al., 2001).

The panel agreed that it would be unusual for a patient to come to transplantation without antecedent indication for antiviral therapy. The need for transplantation defined the preceding level of replication as harmful. It was therefore agreed that patients being listed for transplantation with detectable HBV DNA by commercial PCR assays should be commenced on antiviral therapy. Agreed principles of selecting antiviral therapy were to maximally suppress replication and ensure ongoing viral susceptibility at the time of transplantation to the agent(s) chosen. To ensure this, patients should undergo repeat DNA testing every 3 months in order to screen for emerging antiviral resistance.

2.2.3. Prevention of recurrence post-transplant

Early strategies to prevent graft re-infection used human immunoglobulin with high titres of antibody to HBsAg (known as HBIg). Factors shown to be associated with failure of HBIg prophylaxis included transplantation for cirrhosis (compared with fulminant infection), HBe-antigen positivity and high HBV DNA levels. Those with delta virus co-infection appeared to have a low risk (Samuel et al., 1993). The use of high dose HBIg (to maintain titres >500 IU/ml) reduced the risk of recurrence to between 15% and 35% (McGory et al., 1996; Terrault et al., 1996).

Initially the nucleoside analogue lamivudine was used as monoprophylaxis against graft re-infection. Whilst effective

in the short term, over time high rates of antiviral resistance were observed and emergence of resistant virus was associated with significant graft infection and damage (Lok et al., 2003). With the availability of antiviral therapy which is effective against lamivudine-resistant strains, some centres have adopted a strategy of sequential use of antivirals to manage the problem of lamivudine resistance (Lo et al., 2007). A recent analysis suggested that whilst such a strategy may be cost effective, this is at the risk of increased recurrence and mortality rates (Dan et al., 2006).

The use of both HBIg and lamivudine in combination has led to HBV recurrence rates of less than 10% (Angus et al., 2000; Marzano et al., 2001; Rosenau et al., 2001) and this is now considered the standard of care. A wide variety of HBIg regimes are in successful use and these vary in dosage, routes of administration (intravenous (Markowitz et al., 1998; Han et al., 2000; Marzano et al., 2001; Rosenau et al., 2001; Roche et al., 2003) versus low dose intramuscular (Yao et al., 1999; Yoshida et al., 1999; Angus et al., 2000; Zheng et al., 2006; Gane et al., 2007)), and dosing schedules (fixed dosing (Markowitz et al., 1998; McCaughan et al., 1999; Yao et al., 1999; Angus et al., 2000; Han et al., 2000; Marzano et al., 2001; Zheng et al., 2006; Gane et al., 2007) versus on-demand (Yoshida et al., 1999; Rosenau et al., 2001; Roche et al., 2003)). Until recently the longest published follow-up data existed for intravenous regimes, with median follow-up

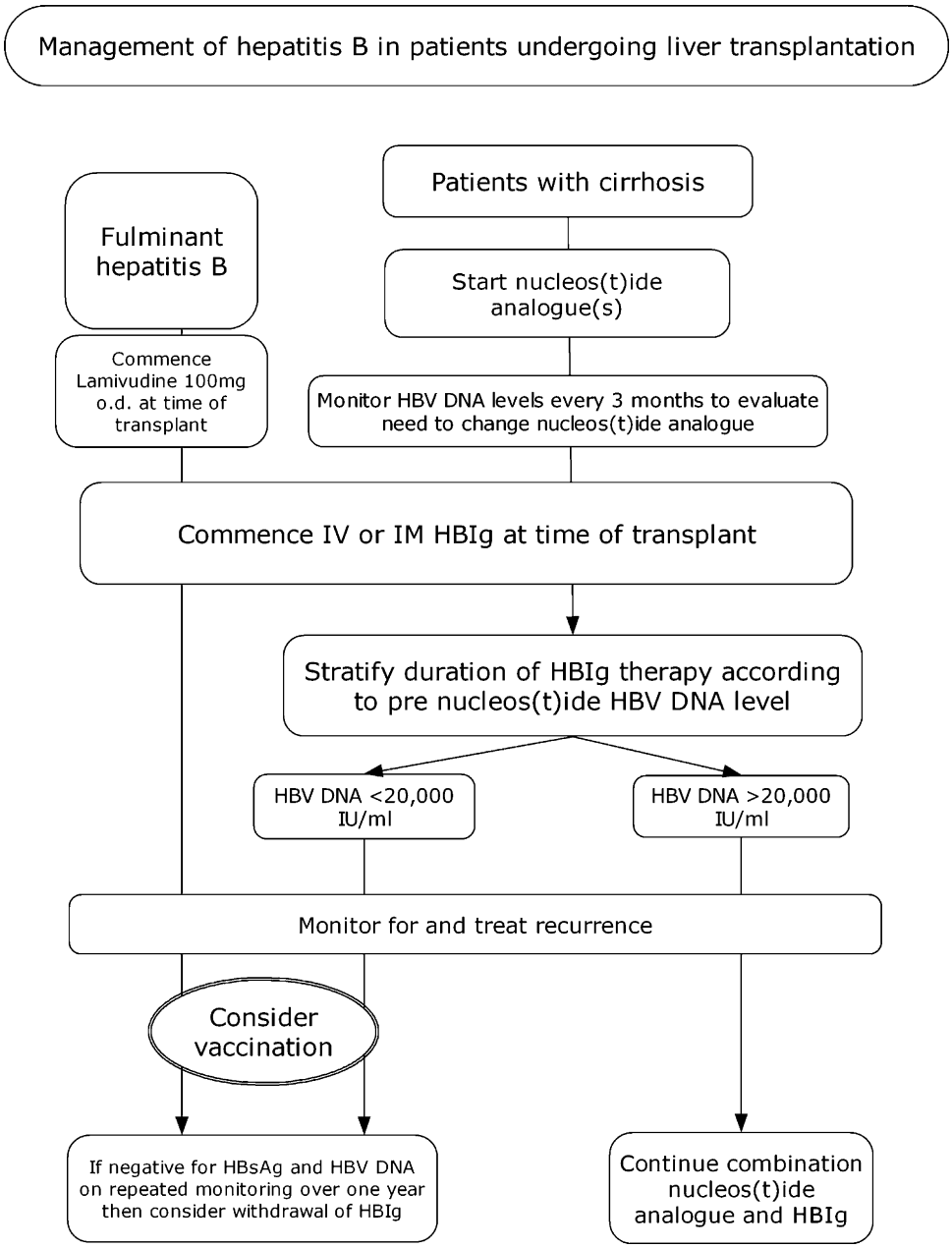

Fig. 2. Algorithm for the management of hepatitis B in patients undergoing liver transplantation.

periods of 30 months and 5 years in the studies by Marzano et al. (2001) and Roche et al. (2003) demonstrating recurrence rates of only 3.8% and 8%, respectively. However, more recently Gane et al. (2007) published results of a cohort of 147 patients from Australia and New Zealand who received either 400 IU/month or 800 IU/month intramuscularly in whom the actuarial risk of recurrence at 5 years was 4%.

Adefovir has also been used in an open label compassionate use study for patients with lamivudine-resistant virus both pre- and post-transplant (Schiff et al., 2007). Amongst the 57 patients coming to transplant HBV recurrence was low with HBsAg detectable on first assay in 6% and 9% of patients who did or did not receive HBIg, respectively. Serum HBV DNA was detected on consecutive visits in 6% and 0% of patients who did or did not receive HBIg, respectively. The authors concluded that adefovir was successful in preventing HBV recurrence in lamivudine-resistant patients regardless of whether HBIg was co-administered, though the study was not designed to compare the differing regimes and follow up was short. At present a multicentre UK trial is underway to establish if adefovir can be substituted for HBIg post-transplant in high-risk patients. Data for HBIg in combination with other nucleos(t)ide analogues is limited but studies using newer analogues, such as entecavir, to prevent recurrence in the post-transplant patient are ongoing.

Reflecting the best evidence for preventing recurrence the authors recommend the combination of HBIg and a nucleos(t)ide analogue to which virus is susceptible to prevent post-transplant recurrence. It is thought likely that in future combination nucleos(t)ide therapy may supplant the use of HBIg.

2.2.4. Withdrawal of HBIg

Issues of cost, availability and patient factors such as tolerability and convenience of administration have led to attempts to identify strategies to allow safe withdrawal of HBIg therapy with continued prophylaxis with a nucleos(t)ide(s) alone. The strategies most commonly pursued have been either to identify those at lowest risk of recurrence, or to vaccinate patients to induce host production of anti-HBs.

Those at low risk of recurrence of HBV include patients transplanted for fulminant hepatic failure and those with low HBV DNA levels prior to instigation of antiviral therapy (Samuel et al., 1993; Gane et al., 2007). Long-term follow-up of 20 patients who had withdrawal of HBIg between 1 and 18 months post-transplant found recurrence in 4 (18%) patients, however, 3 of these cases were felt to relate to poor compliance with therapy (Buti et al., 2006). More recently Wong et al. (2007) reported a retrospective analysis of 21 patients, 3 of whom received 1 week only of HBIg and the remainder a median of 20 months. At a median of 42 months (range 4.5–51) following withdrawal of HBIg only one patient (4.8%) had recurrence.

Attempts to induce anti-HBs titres by vaccination have had varied success. Various measures to enhance host response to vaccine have been attempted, however, comparing differing approaches is difficult due to differences in the viral status of patients, immunosuppressive regimes used and the levels of anti-HBs defined as response. In addition differences in co-administration of lamivudine or HBIg during vaccination have been used to explain differing response rates between otherwise similar studies. The most impressive results using standard recombinant vaccine by Sanchez-Fueyo et al. (2000) have not been replicated (Angelico et al., 2002; Di et al., 2006), whilst third generation recombinant vaccines containing additional pre-S1 and pre-S2 gene products have given mixed results (Karasu et al., 2005; Lo et al., 2007). The most promising results thus far have been those reported by Bienzle et al. (2003), who used a novel adjuvant system to achieve anti-HBs titres of >500 IU/ml in 16/20 (80%) of patients. Further studies, varying the adjuvant used, have proved less successful and further trials are required (Starkel et al., 2005; Rosenau et al., 2006).

It is the authors view that patients at high risk of recurrence should always be maintained on combination antiviral therapy, and that the most robust evidence exists for HBIg in combination with a nucleos(t)ide analogue. Patients at low risk of recurrence, that is those transplanted for fulminant hepatic failure or with low pre-treatment DNA levels, should be considered for HBIg withdrawal after a period of combination prophylaxis, but should be monitored carefully for HBsAg and DNA relapse after HBIg withdrawal. Vaccination can be considered for patients in whom withdrawal is planned, however the optimal vaccine has yet to be identified and decisions about vaccination should be independent of the decision to withdraw HBIg.

2.3. Management of hepatitis B in patients undergoing renal transplantation (Fig. 3)

2.3.1. Background

The incidence of HBV infection in patients coming to renal transplantation continues to fall as a result of immunisation of pre-dialysis and dialysis patients, regular screening for infection and strict infection control measures (Finelli et al., 2005). Despite these measures the prevalence in developed countries is still between 0% and 8% (Burdick et al., 2003). Hepatitis B infection in patients with end stage renal disease (ESRD) is usually asymptomatic even in the acute period and typically up to 80% of patients' progress to a chronic carrier state (Harnett et al., 1988).

2.3.2. Effects of HBV infection on outcome

The influence of HBsAg-positive infection on outcome following renal transplant has been controversial. However a meta-analysis of published trials in 2005 concluded a significantly higher all cause mortality (relative risk 2.49, 95% CI 1.64–3.78) and risk of graft failure (relative risk 1.4, 95% CI 1.02–2.04) (Fabrizi et al., 2005). Most, but not all of the studies, concluded significantly higher risk of death from liver cirrhosis or hepatocellular carcinoma.

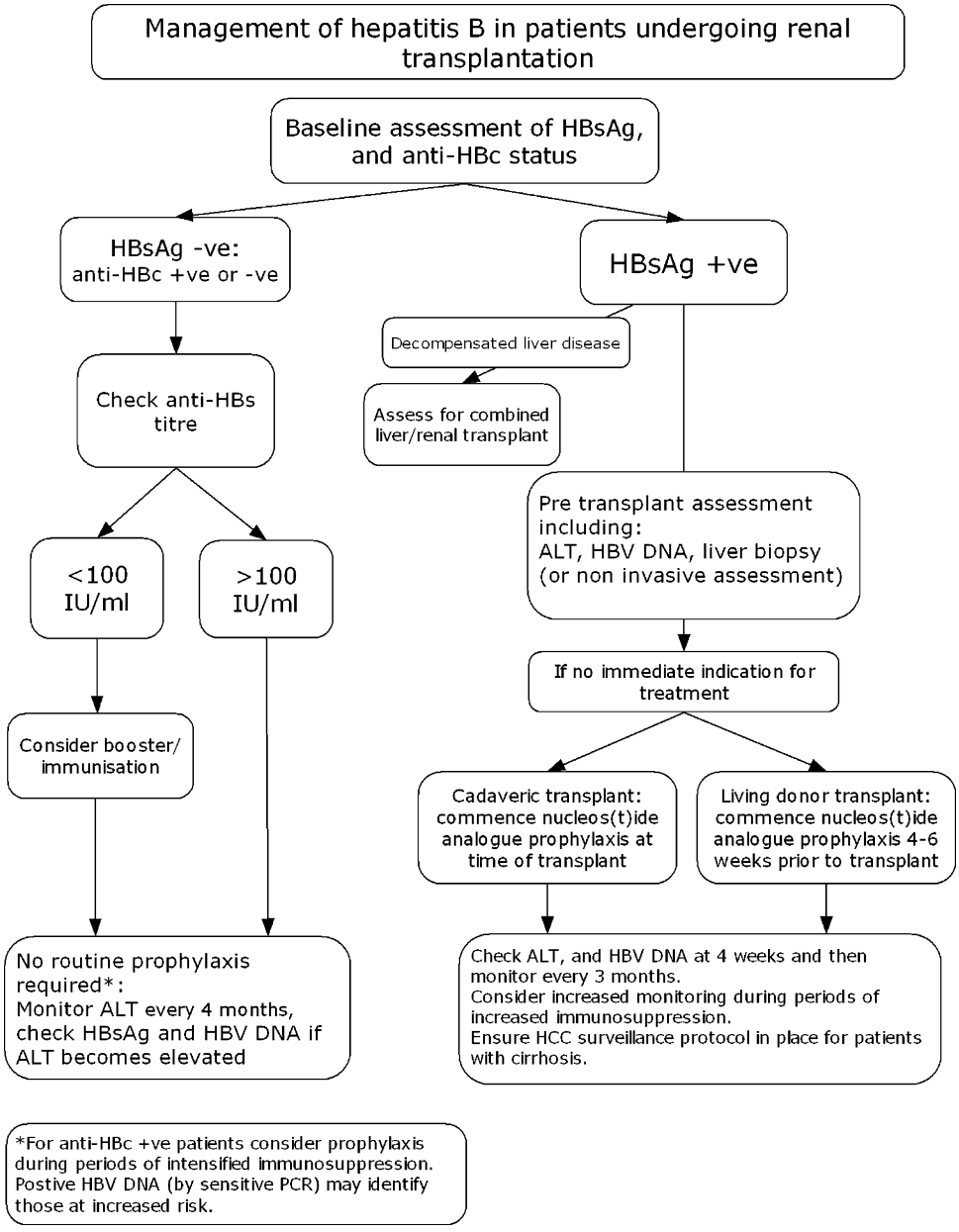

Fig. 3. Algorithm for the management of hepatitis B in patients undergoing renal transplantation.

Mathurin et al. (1999) found a 10-year survival rate of 45% amongst HBsAg-positive patients comparing poorly with both HCV infected patients (65%) and a case matched control population without evidence of HBV or HCV infection (80%). In patients who had a biopsy proven diagnosis of cirrhosis, 10-year survival was as low as 26%.

The largest study to undertake serial liver biopsies in patients positive for HBsAg after renal transplant found histological deterioration in 85.3% of patients, including cirrhosis in 28% at a mean interval of 66 months, no patients having been cirrhotic on baseline biopsy (Fornairon et al., 1996). Amongst those patients with cirrhosis, HCC was found in 23%, suggesting an annual incidence of HCC of between 2.5% and 5%.

2.3.3. Reactivation in HBsAg-negative patients

The risk of reactivation of HBV amongst patients with previously "resolved" infection, that is negative for HBsAg and positive for anti-HBc, is low. Berger et al. (2005) found recurrence (reappearance of HBsAg) in 2/229 (0.9%) of such patients, 1 of whom was asymptomatic. Knoll et al. (2005) presented data looking at recurrence amongst kidney, liver and heart transplant recipients all of whom where HBsAg-negative and anti-HBc-positive pre-transplant. Of 23 such patients receiving a renal transplant only 1 patient (4.3%) developed transient recurrence of HBsAg. More recently Savas et al. (2007) reported two cases of reactivation and provided a review of 25 previously reported cases. They noted a wide age range of patients experiencing recurrence

(22–75 years), a male preponderance and a time of onset post-transplant of between 8 weeks and 15 years. The authors noted that with one exception all patients had anti-HBs titres of less than 100 IU/ml and suggest that vaccination of such patients may be an effective preventative measure. No trials evaluating such an approach were identified.

2.3.4. Assessment prior to transplant

Virtually all patients being assessed will have their HBsAg status previously documented and will have undergone vaccination if negative.

Assessment of HBsAg-positive patients with ESRD is complicated by a number of issues. Serum transaminase levels are lower than in non-uraemic populations with the normal cut off for ALT being estimated as low as 17 IU/l (Hung et al., 1997). Whilst dialysis patients with positive HBsAg are likely to have higher ALT values than those who are negative (Fabrizi et al., 2002), transaminase levels may not equate with histological findings (Rodrigues et al., 1997). In addition HBV DNA measurements are less well validated in patients with ESRD. Fabrizi et al. (2003) demonstrated that whilst HBsAg-positive patients with detectable HBV DNA had significantly higher levels of ALT than those who were negative (mean 19 IU/ml versus 12 IU/ml), overall DNA levels were low (mean 4.09×10^2 copies/ml) and the correlation with disease progression remains uncertain.

Serological markers of fibrosis such as the commercially available Fibrotest panel have been evaluated in ESRD and transplant patients with similar efficacy to other populations and may remove the need for liver biopsy in approximately 1 in 3 patients (Imbert-Bismut et al., 2001; Varaut et al., 2005). Theoretically non-invasive tests using transient elastography may be less accurate in uraemic patients due to increased skin stiffness, but data is limited. Given the uncertainties surrounding interpretation of transaminase and HBV DNA levels liver biopsy is often required to assess the severity of liver disease.

It was the view of the panel that with the advent of potent antiviral therapy, cirrhosis in itself should no longer be considered a contraindication to renal transplantation. However, patients with decompensated liver disease should however continue to be assessed for combined liver and renal transplantation.

2.3.5. Management post-transplant—antiviral therapy

The evidence for using interferon alpha post renal transplant is limited but available data suggest a high associated risk of graft rejection, precluding its use (Durlik et al., 1995). Likewise issues regarding efficacy and tolerability limit its use in ESRD patients being considered for transplant (Rodrigues et al., 1997).

The largest body of evidence in the renal transplant setting is for lamivudine with a meta-analysis by Fabrizi et al. (2004) demonstrating rates of HBV DNA and HBe-antigen clearance of 91% and 72%, respectively. Resistance rates across the trials were significant at 18% after median treatment duration of 18 months. Studies evaluating the benefits of prophylactic lamivudine versus treatment only on reactivation suggest that with the latter approach the majority of patients will end up on treatment (Chan et al., 2002) and may have a worse outcome than those treated prophylactically (Filik et al., 2006).

Limited data is available regarding use of the newer antivirals in renal transplant patients. One small study by Fontaine et al. (2005) suggests that adefovir, is safe and as effective as in non-transplanted patients. Like adefovir and lamivudine, entecavir requires dose adjustment according to creatinine clearance. No data regarding its use in renal transplant patients was identified.

Given the high risks of reactivation and disease progression amongst HBsAg-positive patients it was the view of the meeting that all such patients should be treated with antiviral therapy and as in other situations the choice of this should reflect the goals of maximally suppressing viral replication and minimising resistance. It was suggested that in the absence of other indications for treatment patients undergoing live donor transplantation should commence antiviral prophylaxis 4–6 weeks prior to transplantation and that in cadaveric organ recipients treatment may be deferred until the time of transplant.

Given the low risk of reactivation of patients who are HBsAg negative it is not recommended that universal prophylaxis is given. Limited evidence suggests that amongst those positive for anti-HBc, those with low titres of anti-HBs (<100 IU/ml) are at greatest risk and repeat vaccination should be considered for this group. Amongst those with isolated anti-HBc-positive serology sensitive HBV DNA assays may detect those with true occult infection. However data on the absolute risk of reactivation is lacking and it is unclear if prophylaxis is warranted.

2.3.6. Management post-transplant—other considerations

As in other settings monitoring for treatment failure and the development of resistance is crucial and initially this should be performed every 3–4 months. Closer observation of the patient should be considered during changes in immunosuppression which may precipitate reactivation. The panel were of the opinion that nucleos(t)ide analogue prophylaxis should be considered in HBsAg-negative/anti-HBc-positive patients during periods of escalation of immunosuppression, for example the treatment of rejection.

2.4. Hepatitis B and HIV co-infection (Fig. 4)

2.4.1. Background

Approximately 9% of HIV-infected patients in Europe have co-infection with hepatitis B (Konopnicki et al., 2005). It might have been expected that HIV-related immune dysfunction would lead to a more benign course of liver disease in those patients with co-infection. However the evidence is that co-infection leads to a more aggressive course of liver

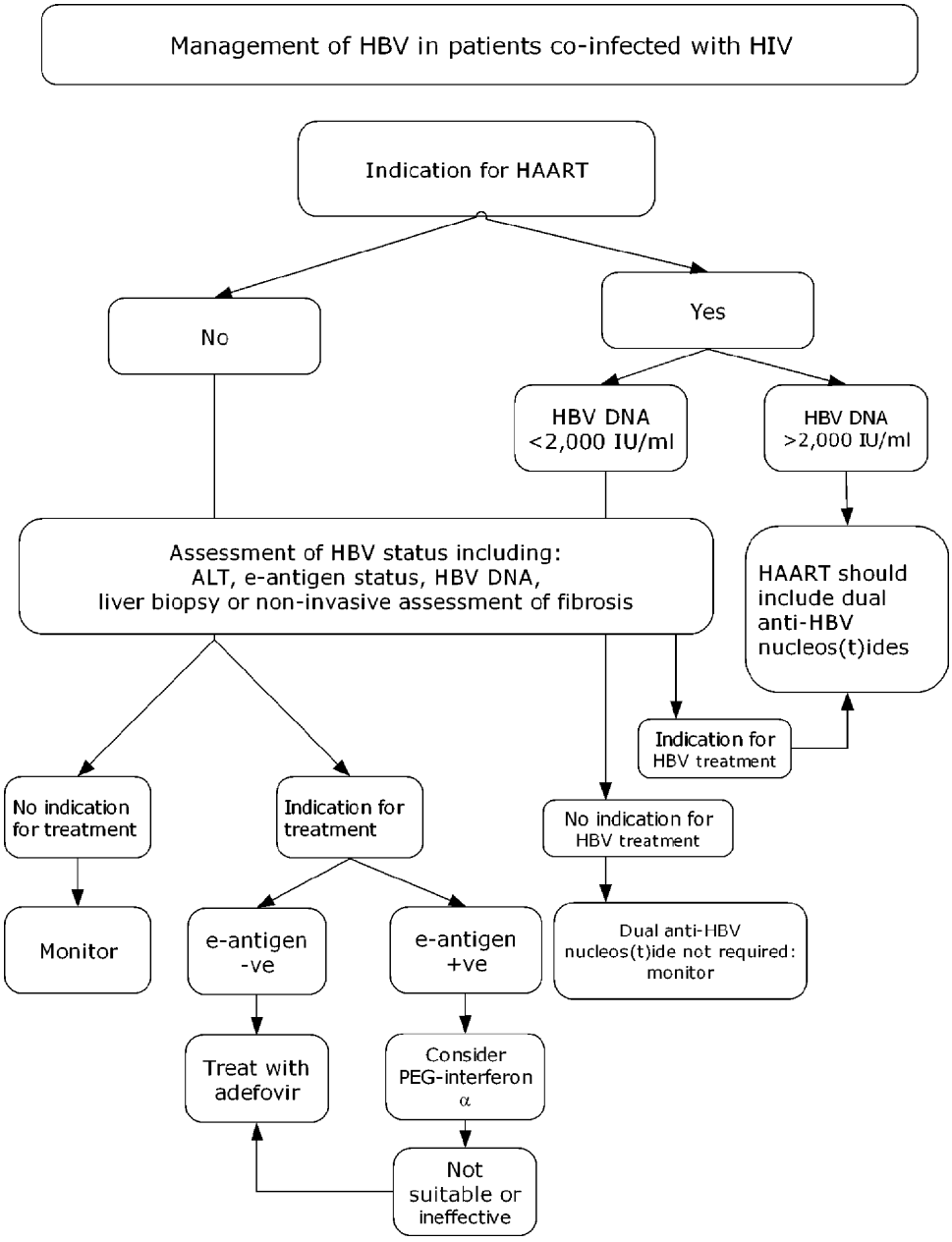

Fig. 4. Algorithm for the management of hepatitis B in patients co-infected with HIV.

disease (Puoti et al., 2006), with patients demonstrating both higher liver related and all cause mortality compared to those with HIV mono-infection (Thio et al., 2002; Konopnicki et al., 2005).

Excellent management guidelines for HBV/HIV co-infection exist including those resulting from a 2004 consensus conference held in North America (Soriano et al., 2005), the 1st European consensus on the treatment of chronic hepatitis B and C in HIV co-infected patients (Benhamou, 2006) and the British HIV association guidelines on co-infection with HIV and hepatitis B virus infection (Brook et al., 2005), to which we would direct the reader. We provide a brief summary on HIV co-infection and a treatment algorithm is presented in Fig. 4.

2.4.2. Assessment of HBV status

As in the mono-infected patient HBV assessment includes measurement of ALT, e-antigen status and HBV DNA levels. Serum ALT levels are lower than in mono-infected patients, however, this does not necessarily correlate with hepatic inflammation and therefore ALT is less useful in predicting significant liver disease (Colin et al., 1999). Likewise the significance of DNA levels in co-infected patients is less well defined and guidelines tend to follow those for mono-infected patients. These difficulties mean that liver biopsy is often required to assess need for treatment. Non-invasive tests for hepatic fibrosis, either biochemical or using elastography, may be considered but have yet to be fully validated in the co-infectedpatient.

2.4.3. Treatment

Appropriate treatment is dependent on whether there are indications to treat HBV, HIV or both. In each of these situations the guiding principle is to minimise viral resistance by avoiding regimes that contain only one agent effective against a particular virus. In addition to the antivirals licensed for HBV mono-infection, the nucleos(t)ide analogues tenofovir and emtricitabine, which are licensed for HIV infection, are also effective against HBV (Ristig et al., 2002; Gish et al., 2005; Lim et al., 2006; Benhamou et al., 2006a).

For patients requiring treatment of both HBV and HIV a HAART regime including two agents with anti-HBV activity should be used, typically involving tenofovir with either lamivudine or emtricitabine. Regimes that include single agents active against HBV, in particular those with poor resistance profiles such as lamivudine or emtricitabine should be avoided.

Amongst those patients with an indication for HIV therapy alone, those with high HBV DNA levels (>2000 IU/ml) require treatment regimes as above in order to minimise the risk of an immune reconstitution hepatitis. Those with DNA levels <2000 IU/ml and no other indication for treatment, for example cirrhosis, do not need regimes with dual activity but should have regular monitoring of viral status. It is important that increased consideration be given to the patients HBV status prior to changes being made to a HAART regime, in particular where a nucleos(t)ide with anti-HBV activity is due to be withdrawn.

For those patients with an indication for treatment of HBV alone the options are somewhat limited, although in the panels experience such patients are relatively uncommon. Adefovir at a dose of 10 mg daily has been shown to be effective in co-infected patients and does not induce HIV resistance mutations (Delaugerre et al., 2002; Benhamou et al., 2006b). Initial evidence for entecavir's effectiveness in co-infected patients has been tempered by evidence of induction of HIV resistance mutations (Colono et al., 2006; McMahon et al., 2007). For those patients who are e-antigen positive then pegylated interferon alpha can be considered. The evidence for interferon alpha relates to non-pegylated preparations in trials predating the widespread use of HAART (Wong et al., 1993). These suggested decreased effectiveness compared to its use in mono-infected patients and further studies in the context of current HIV therapy are required.

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